

## Pre-transplantation assessment of renal viability with $^{31}\text{P}$ magnetic resonance spectroscopy

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**Pre-transplantation assessment of renal viability with  $^{31}\text{P}$  magnetic resonance spectroscopy.** As acute tubular necrosis (ATN) is still an important cause for postoperative malfunction of renal grafts, it would be useful to have a method predicting such a complication. We investigated the possibility to predict ATN by measuring the ratio of phosphomonoesters (PME, largely consisting of adenosine monophosphate) and inorganic phosphate (Pi) in the renal tissue, using  $^{31}\text{P}$  magnetic resonance spectroscopy (MRS) during the cold ischemia period. Assuming that this ratio reflects the tissue high-energy phosphate status, we studied five kidneys from living related donors (LRD), 28 kidneys from heart beating donors (HBD) and nine kidneys from non-heart beating donors (non-HBD). All kidneys were preserved with a phosphate free solution. We found an inverse relation between the time of  $^{31}\text{P}$  MRS and the PME/Pi ratio, suggesting a graded decay of tissue high energy phosphates during cold ischemia. The PME/Pi ratio was highest in grafts from LRD ( $2.65 \pm 0.50$ , no ATN), intermediate in grafts from HBD ( $1.65 \pm 0.41$ , 21% ATN) and lowest in those derived from non-HBD ( $1.05 \pm 0.47$ , 56% ATN). The differences in PME/Pi ratio between the groups was statistically significant ( $P < 0.01$ ). Moreover, the ratio was significantly lower in grafts developing ATN ( $1.73 \pm 0.41$  vs.  $1.35 \pm 0.29$  in the HBD group,  $1.41 \pm 0.24$  vs.  $0.76 \pm 0.36$  in the non-HBD group,  $P < 0.05$ ). These observations point to a general relation between the pre-transplant kidney PME/Pi ratio and the development of ATN. However, the predictive value of a low PME/Pi ratio was too low (36%) to reliably predict development of ATN in individual cases. Extrapolation of the PME/Pi ratio to the time of nephrectomy increased the predictive value to 67%.

In about 30% of all renal transplantations the graft shows a delayed function, whereas in about 5% the transplant never starts functioning at all [1]. When organs of donors who have been in shock or have experienced a cardiac arrest are used, the incidence of primary malfunction due to acute tubular necrosis (ATN) increases. In kidneys derived from non-heart beating donors, the percentage of delayed function is about 75%, while 12.5% will never function [2]. Apart from the condition of the donor, factors such as the procedure of the explantation and preservation, the type of preservation fluid, the duration of cold and warm ischemia, and the condition of the recipient may determine the postoperative function of the graft. A non-invasive method to predict ATN before transplantation could be helpful in the management of the patient after implantation.

During cold storage of the graft, the high-energy phosphates adenosine triphosphate (ATP) and adenosine diphosphate (ADP) are degraded [3, 4]. This is reflected by an increase in adenosine monophosphate (AMP) and inorganic phosphate (Pi). AMP is catabolized to adenosine and inorganic phosphate, adenosine to inosine and this finally to hypoxanthine. After reperfusion, hypoxanthine serves as an oxidable substrate for xanthine oxidase, whereby the free radical superoxide is produced within a few minutes [5]. This sequence of events may lead to organ damage and dysfunction through several mechanisms. Lack of ATP and ADP may damage the cell by restraining energy needing pumps, like the Na-K-ATPase, which may cause cell swelling [3]. Furthermore, adenosine is a powerful renal vasoconstrictor [6], and might be one of the factors leading to ATN. Finally, free radicals like superoxide can disrupt cell function in several ways, such as by inactivating Na-K-ATPase, degradation of DNA and interrupting the lipid bilayer of the cell membrane [3]. Consequently, it is conceivable that the levels of ATP and its breakdown products in the preserved graft are related to the postoperative function of the graft.

$^{31}\text{P}$  magnetic resonance spectroscopy ( $^{31}\text{P}$  MRS) is a non-invasive technique which allows *in vitro* measurement of relative or absolute tissue concentrations of phosphorus containing metabolites, such as ATP, AMP and Pi. Bretan et al have used  $^{31}\text{P}$  MRS to study kidney graft viability [7]. They found a lower phosphomonoester/inorganic phosphate ratio (PME/Pi ratio) in kidneys showing delayed graft function due to ATN. The PME peak in a  $^{31}\text{P}$  MR spectrum is largely formed by AMP. A reduced PME/Pi ratio could therefore be due either to a reduced AMP content or an increased Pi concentration, both of which have been demonstrated by biochemical analysis in ischemic kidneys [8]. The results of  $^{31}\text{P}$  MRS measurements in kidney grafts appear to be dependent on the Pi content of the preservation fluid, as it has been found that lower PME/Pi ratios are measured in kidneys preserved in fluid with a high free phosphate content (Euro-Collins, [Pi] 57 mmol/liter) compared to organs preserved in fluid with a lower Pi content (University of Wisconsin fluid, [Pi] 25 mmol/liter) [9]. This was confirmed by Ciancabilla et al, who found an inverse relation between PME/Pi ratio and the preservation fluid phosphate content in a study in rabbits [10]. These authors concluded that it is necessary to establish reference values for each type of preservation fluid.

We therefore decided to perform  $^{31}\text{P}$  MRS measurements in kidneys preserved in a non-phosphate containing preservation fluid. Histidine-tryptophan-ketoglutarate (HTK) is such a fluid,

Received for publication January 31, 1994

and in revised form May 26, 1994

Accepted for publication July 11, 1994

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with a post-operative graft function at least comparable to that obtained with the UW solution [1]. The goal of this study was to determine the relation between PME/Pi ratio in HTK fluid preserved kidneys and direct postoperative graft dysfunction due to ATN in a prospective fashion.

## Methods

### Donors and recipients

Forty-two kidneys were derived from 33 donors: 5 from living related donors (LRD), 28 from 22 heart beating donors (HBD) and 9 from 6 non-heart beating donors (non-HBD). The age of the donors ranged from 7 to 71 years. Causes of death in the HBD group were: intracerebral bleeding ( $N = 7$ ), cerebral ischemia ( $N = 6$ ) and skull trauma ( $N = 9$ ). Based on the presence of a cardiac arrest (initial recovery,  $N = 3$ ) and/or a serum creatinine concentration  $>120 \mu\text{mol/liter}$  ( $N = 4$ ), we divided the HBD group into a group with an unfavorable (7 kidneys from 5 donors) and a favorable (21 kidneys from 17 donors) prognosis concerning direct post-operative graft function. Ten nephrectomies were performed in our hospital, and 12 elsewhere in the Eurotransplant region. The causes of death in the non-HBD group were: intracerebral bleeding ( $N = 1$ ), primary cardiac arrest ( $N = 1$ ) and skull trauma ( $N = 4$ ). Five donors experienced a prolonged period of shock in the hours before nephrectomy and in one the serum creatinine concentration was  $>120 \mu\text{mol/liter}$ . Five non-HBD came from our hospital and were treated before the cardiac arrest on an intensive care unit. One kidney came from a donor in Maastricht, the Netherlands, who sustained a primary cardiac arrest upon arrival on the emergency ward. All non-HBD kidneys were perfused *in situ* using a double balloon triple lumen catheter as described by Booster et al. [2]. Warm ischemia time in these kidneys varied between 25 and 45 minutes. All kidneys were perfused with HTK (Custodiol<sup>®</sup>) and packed according to standard Eurotransplant instructions.

Twenty-eight implantations were performed in our hospital: 5 of 5 transplants from LRD, 20 of 28 from HBD and 3 of 9 from non-HBD. All recipients in our hospital were adults (ages ranging from 18 to 64 years). The immunosuppressive protocol in our patients consisted of cyclosporine A and low dose prednisone. Post-operative function was determined by urine production and serum creatinine determinations. To detect rejection and vascular or urological complications, duplex-echography and  $^{88\text{m}}\text{Tc}$ -MAG3 scintigraphy were performed bi-weekly in all patients in the first two weeks. In case of persisting oligo- or anuria, a renal biopsy was taken after one week. The other 14 kidneys were transplanted within the Eurotransplant region, mostly in adults. Different immunosuppressive protocols were used in the recipients of these grafts. Information on their postoperative course was obtained by questionnaire. Delayed graft function due to ATN was defined as the necessity of dialysis in the first week after transplantation, after exclusion of other causes for dysfunction, like hyperacute rejection, vascular thrombosis or urinary leakage.

### $^{31}\text{P}$ MRS measurements

$^{31}\text{P}$  MRS was performed during the cold ischemia preservation period, on a Philips gyrosan S15, operating at 1.5 Tesla. Prior to  $^{31}\text{P}$  MRS, the magnetic field homogeneity was optimized by shimming on the  $\text{H}_2\text{O}$  proton signal, using the regular head coil provided by the manufacturer. For  $^{31}\text{P}$  MRS we used a double

Helmholz coil with two loops of 15 cm, which was placed octagonally inside the regular head coil. We used a frequency-modulated adiabatic rapid half passage pulse as detection pulse (adiabatic pulse length 3 msec). This pulse created a non-selective 90 degree excitation inside the whole coil. The kidney remained in its sterile bag filled with HTK solution. This bag was placed into another plastic bag filled with ice to cool the organ. Care was taken to place all kidneys inside the coil in approximately the same position. Partial saturation spectra with a repetition time of 2000 msec, 256 acquisitions, 3000 Hz sample frequency and 2048 sample points were recorded. The total examination time was 30 minutes. The averaged free induction decays were zero filled to 4096 data points and processed with a convolution difference procedure (150 Hz) and exponential multiplication (6 Hz). After Fourier transformation, a linear phase correction was applied.

Six  $^{31}\text{P}$  peaks were identified for fitting: the phosphomonoester peak (PME), the inorganic phosphate peak (Pi), the phosphodiester peak (PDE), and three phosphoryl peaks of adenosine triphosphate ( $\gamma$ ,  $\alpha$  and  $\beta$  ATP). Individual  $^{31}\text{P}$  spectra were fitted by Gaussian lineshapes with a least squares method (NMR1 program, New Methods Research, Syracuse, New York, USA) to determine chemical shifts and metabolic peak integrals. Since the ATP resonances were often hard to detect or showed a low signal to noise ratio ( $<5$ ), only the PME/Pi ratio was used for calculations.

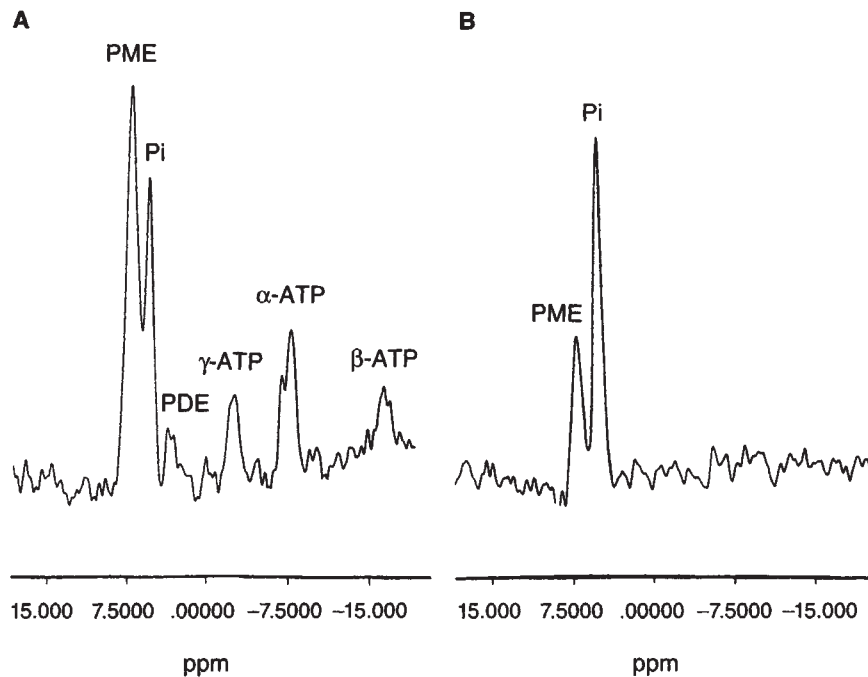
### Statistics and calculations

Patients were classified as recipients of kidneys from LRD, HBD and non-HBD, showing either immediate or delayed graft function. Data are expressed as the mean  $\pm$  standard deviation. Analysis of differences in mean values in the three groups (LRD, HBD and non-HBD) was performed by one-way analysis of variance (ANOVA). If variation ratios were statistically significant ( $P < 0.05$ ), the differences between the means were analyzed by two-tailed Student's *t*-test for unpaired observations using Bonferroni's protection. Differences between subgroups of patients with or without ATN were tested for statistical significance by the two-tailed Student's *t*-test.

We also performed linear regression and correlation analysis for PME/Pi and the time between nephrectomy and  $^{31}\text{P}$  MRS (time to scanning). To describe the natural time course of the changes in PME/Pi ratio in human kidney grafts, we restricted this analysis to HBD-derived kidneys showing immediate graft function. On the basis of this analysis, we extrapolated the PME/Pi ratio to the time of nephrectomy as well as implantation. Following this analysis, the differences between the groups were tested again for statistical significance as described above. Sensitivity, specificity, positive and negative predictive values of the  $^{31}\text{P}$  MRS method in predicting post-transplant graft dysfunction due to ATN were calculated according to Bayes theorem [11].

## Results

Figure 1A shows a typical  $^{31}\text{P}$  MR spectrum of a kidney from a living related donor, measured within the first hour after nephrectomy. This kidney started to function immediately after implantation. Figure 1B shows a typical spectrum of a kidney with delayed graft function. The ATP peaks are not visible and the PME/Pi ratio is much lower than in Figure 1A. This kidney was



**Fig. 1.** A.  $^{31}\text{P}$  MRS of a kidney perfused with HTK during cold storage, derived from a living related donor with immediate function after implantation. Abbreviations are: PME, monophosphate peak, mainly formed by AMP; Pi, inorganic phosphate peak; PDE, phosphodiester peak. ATP is represented in the  $\gamma$ -,  $\alpha$ - and  $\beta$ - peak, and ADP in the  $\gamma$  and  $\alpha$  peaks. B.  $^{31}\text{P}$  MRS of a kidney perfused with HTK during cold storage derived from a non-heart beating donor; the kidney suffered from severe ATN after transplantation. In contrast to the left hand panel no  $\gamma$ -,  $\alpha$ - and  $\beta$ -peaks are detectable, and the Pi peak is higher than the PME peak.

**Table 1.** Results of PME/Pi ratio, measured and extrapolated

	N	Measured PME/Pi	Extrapolated		Time to scanning	Cold ischemia time
			PME/Pi nephrectomy	PME/Pi implantation		
					hours	hours
LRD	5	$2.56 \pm 0.50^{\text{ab}}$	$2.59 \pm 0.50^{\text{ab}}$	$2.53 \pm 0.50^{\text{ab}}$	$1 \pm 0$	$2 \pm 0$
HBD	28	$1.65 \pm 0.41^{\text{b}}$	$2.03 \pm 0.29^{\text{b}}$	$1.25 \pm 0.38^{\text{b}}$	$14 \pm 10$	$28 \pm 8$
Non-HBD	9	$1.05 \pm 0.47$	$1.28 \pm 0.40$	$0.55 \pm 0.42$	$8 \pm 9$	$26 \pm 5$
HBD ATN-	22	$1.73 \pm 0.41^{\text{c}}$	$2.21 \pm 0.29^{\text{c}}$	$1.21 \pm 0.29^{\text{c}}$	$13 \pm 11$	$28 \pm 9$
HBD ATN+	6	$1.35 \pm 0.29$	$1.89 \pm 0.18$	$0.85 \pm 0.27$	$15 \pm 9$	$29 \pm 6$
Non-HBD ATN-	4	$1.41 \pm 0.24^{\text{d}}$	$1.60 \pm 0.24$	$0.76 \pm 0.24^{\text{d}}$	$5 \pm 1$	$23 \pm 3$
Non-HBD ATN+	5	$0.76 \pm 0.36$	$1.11 \pm 0.41$	$0.17 \pm 0.30$	$11 \pm 11$	$29 \pm 5$

Abbreviations are: LRD, living related donor; HBD, heart beating donor; ATN, acute tubular necrosis; PME, phosphomonoesters; Pi, organic phosphate; N, number of observations.

<sup>a</sup> Difference between LRD and HBD,  $P < 0.01$  (ANOVA)

<sup>b</sup> Difference between LRD or HBD and non-HBD,  $P < 0.01$  (ANOVA)

<sup>c</sup> Difference between (HBD, ATN-) and (HBD, ATN+),  $P < 0.05$  (Mann-Whitney test)

<sup>d</sup> Difference between (non-HBD, ATN-) and (non-HBD, ATN+),  $P < 0.05$  (Mann-Whitney test)

derived from a non-heart beating donor and  $^{31}\text{P}$  MRS was performed 30 hours after nephrectomy; it started to function after one month of anuria.

In all recipients of LRD kidneys immediate post operative function was observed. Delayed graft function due to ATN was found in 21% in the HBD group, and in 56% in the non-HBD group. As shown in Table 1 and Figure 2A, kidneys from LRD had a higher mean PME/Pi ratio than kidneys from HBD or non-HBD ( $P < 0.01$ ). Also, the mean value in the HBD group was greater than in the non-HBD group ( $P < 0.01$ ). Moreover, both within the HBD and the non-HBD group, kidneys from patients with ATN had a lower mean PME/Pi ratio than those with immediate function ( $P < 0.05$ ).

Figure 3 shows the PME/Pi ratios of the kidneys with immediate function, derived from HBD, plotted against the time to scanning. In this subgroup of kidneys, we found a significant

inverse relation between these variables ( $N = 22$ ; slope  $-0.028$ ;  $r = -0.74$ ,  $P < 0.001$ ). We also performed repeated measurements in two kidneys derived from a single non-heart beating donor (Fig. 4). As these kidneys were not implanted because of bad preservation conditions, we were able to measure PME/Pi ratios up to 180 hours after nephrectomy. Although performed at a much lower initial PME/Pi ratio, we also found a linear decay in PME/Pi ratio with increasing time to scanning in this experiment. The slope of the line in each kidney was  $-0.024$ , which is remarkably close to the value observed in the HBD group.

As the times to scanning as well as cold ischemia periods of the various transplantation procedures were quite different (Table 1), we extrapolated PME/Pi values to the time of nephrectomy as well as implantation according to the relation obtained in the HBD group. The extrapolation to the time of nephrectomy hardly affected the PME/Pi ratio of the LRD kidneys, as they were



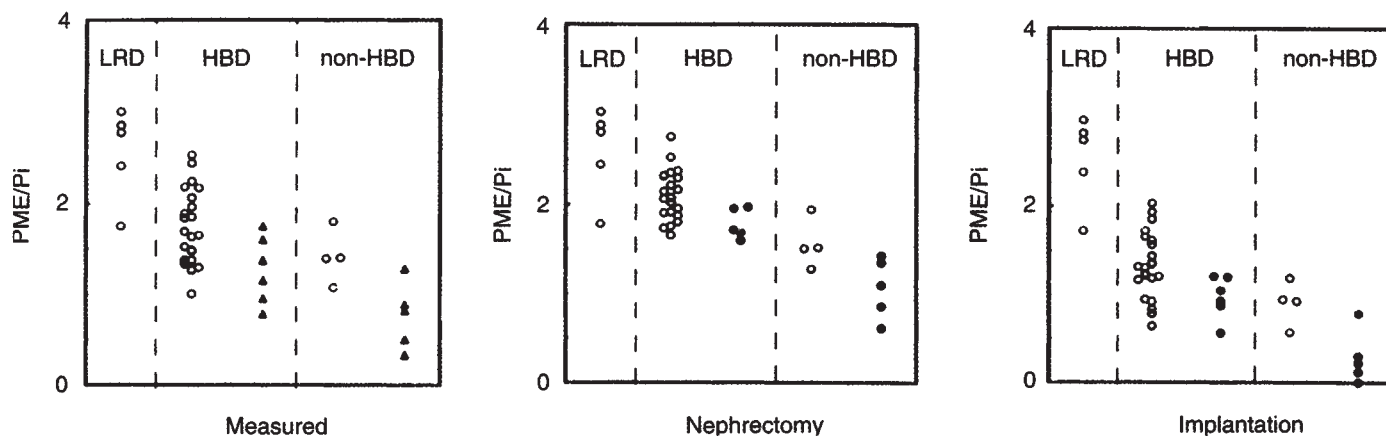


Fig. 2. PME/Pi ratios measured and calculated for the time of nephrectomy and implantation, respectively. Abbreviations are: LRD, living related donors; HBD, heart-beating donors; non-HBD, non heart-beating donors; ATN, acute tubular necrosis. Open symbols represent kidneys with immediate graft function, closed symbols identify kidneys with delayed graft function.

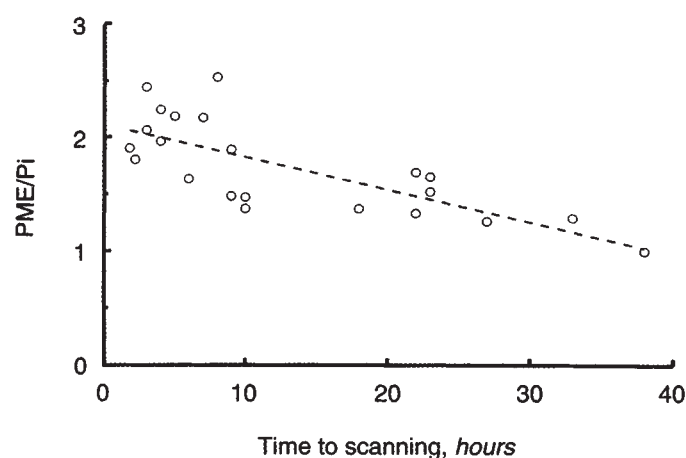


Fig. 3. Relation between PME/Pi ratio and time to scanning (period between nephrectomy and  $^{31}\text{P}$  MRS) in kidney grafts derived from heart beating donors which functioned immediately after implantation.

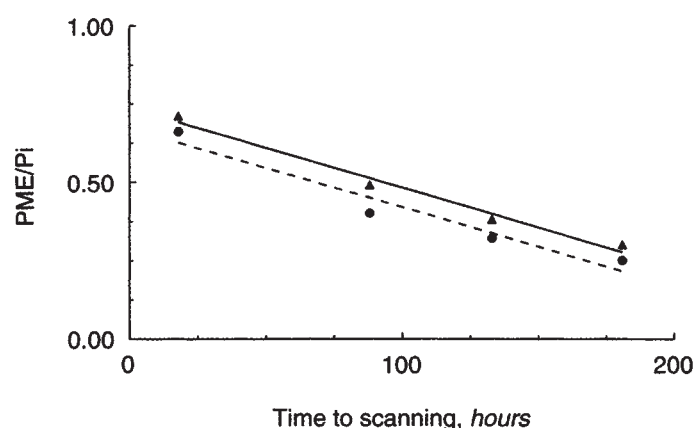


Fig. 4. Repeated measurements in two kidneys from the same (non-heart beating) donor within the first 180 hours after nephrectomy.

measured immediately after nephrectomy and implanted within two hours. As the differences in time to scanning were the greatest in the HBD group, the extrapolation caused a decrease in variation coefficient from 25% (measured PME/Pi ratios) to 14% (PME/Pi ratios estimated at the time of nephrectomy). When calculated for the time of nephrectomy, the difference in mean PME/Pi ratio for LRD and HBD kidneys decreased (compare Fig. 2A and B; Table 1). In general differences in group means for the PME/Pi ratio increased after extrapolation to the time of implantation (Table 1).

Table 2 shows the sensitivity, specificity, efficacy and predictive values of the test for the measured as well as extrapolated PME/Pi values of the HBD group. The best predictive values of  $^{31}\text{P}$  MRS for detecting ATN in HBD-derived kidneys were found in the data extrapolated to the time of nephrectomy. The number of kidneys derived from non-HBD was too low to perform these calculations for this group.

We also classified the HBD kidneys according to the presence or absence of cardiac arrest or increased serum creatinine level in the donor. We did not find a difference in measured or extrapo-

Table 2. Sensitivity, specificity, efficacy and predictive values of  $^{31}\text{P}$  NMR for detecting acute tubular necrosis in kidneys derived from heart beating cadaveric donors

	Measured	Nephrectomy	Implantation
Threshold	1.71	1.75	0.95
Sensitivity	83%	67%	67%
Specificity	59%	91%	77%
Efficacy	53%	86%	75%
Positive predictive value	36%	67%	44%
Negative predictive value	93%	91%	89%

lated PME/Pi between the two prognostic groups: when extrapolated to the time of nephrectomy, mean PME/Pi in the kidneys from the unfavorable prognostic group was  $1.78 \pm 0.49$  ( $N = 7$ ), as opposed to  $1.60 \pm 0.38$  ( $N = 21$ ) in the potentially favorable group. In the former group delayed graft function was seen in 2 out of 7 kidneys (29%), while this was the case in 4 of the 21 grafts (19%) in the former group (NS). We were not able to find a significant relation between the incidence of ATN and the length of the cold ischemia period in our small group of patients.

The results of paired  $^{31}\text{P}$  MRS measurements ( $N = 9$ ) in

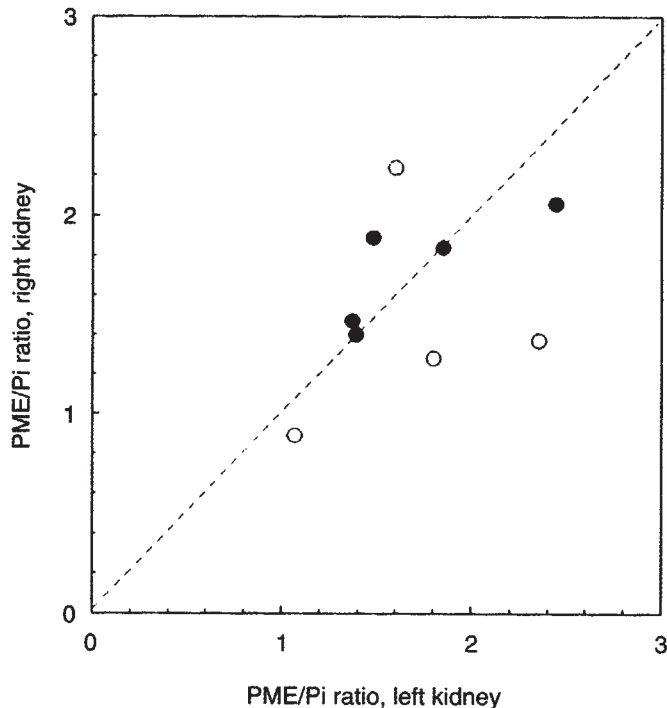


Fig. 5. Results of PME/Pi measurements in nine pairs of kidneys. The dotted line is the line of identity. Open symbols indicate pairs of kidneys of which the kidney with the lowest PME/Pi ratio showed delayed function due to acute tubular necrosis.

kidneys derived from the same donor are shown in Figure 5. In three pairs, the difference between the lowest and highest PME/Pi was negligible. Both kidneys derived from these donors functioned immediately. In the other six pairs, the difference between lowest and highest PME/Pi ratio varied from 15% to 43%. In two of these pairs, both kidneys functioned immediately. In the remaining pairs, one kidney showed immediate and one delayed function, the latter always occurring in the kidney with the lowest PME/Pi value.

### Discussion

The main finding of the present study is that there appears to be a relation between a measure of kidney graft high energy phosphate status, the PME/Pi ratio, and graft dysfunction due to ATN. The mean PME/Pi ratio was highest in kidneys derived from LRD (no ATN), intermediate in those derived from HBD (21% ATN) and lowest in kidneys originating from non-HBD (56% ATN). Moreover, the mean PME/Pi ratio in the HBD and non-HBD group was lower in kidneys developing ATN. In contrast, we were unable to find a relation between donor-related prognostic factors and post-operative graft function of HBD-derived kidneys, nor did we find a relation between ATN and cold ischemia time.

The dissimilar PME/Pi ratios observed in the three groups are most likely due to differences in the clinical condition of the donors, which was obviously much better in LRD than in non-HBD, as well as variations in warm ischemia time. Despite the overall agreement between the PME/Pi ratio and the occurrence of ATN in groups of patients,  $^{31}\text{P}$  MRS appeared to be of limited value in predicting development of ATN in individual cases. The

values for the PME/Pi ratio were widely scattered in all groups (Fig. 2A), and a considerable overlap occurred within the groups for kidneys showing either direct or delayed graft function. As a consequence, the positive predictive value of a PME/Pi ratio  $<1.71$  with respect to the occurrence of ATN was only 36% (Table 2). Because we found an inverse relation between PME/Pi ratio and the time between nephrectomy and  $^{31}\text{P}$  MRS, part of the scatter and overlap could be due to the considerable differences in these times. When we eliminated this factor by extrapolation of the PME/Pi ratios to the time of nephrectomy, the overlap and scatter were indeed reduced (Table 1, Fig. 3B), and the positive predictive value of the PME/Pi ratio in HBD-derived kidneys increased to a more acceptable level of 67%.

As the cold ischemia time could be an independent risk factor for ATN, we also extrapolated the PME/Pi ratio to the time of implantation. This procedure, however, did not improve the usefulness of the method, as the positive predictive value remained virtually unchanged (44%). These findings seem to indicate that the high energy phosphate status of the graft at the time of nephrectomy is a more important determinant of postoperative function than at the time of implantation. However, this conclusion is based on indirect, extrapolated data, and hence should be considered with caution.

A considerable proportion of kidneys, both in the HBD and non-HBD groups, showed direct function at PME/Pi ratios considerably lower than in the LRD group. This clearly suggests that other factors than the high-energy phosphate status as assessed by  $^{31}\text{P}$  MRS determine whether ATN will occur. It should be considered, for instance, that terminal products of the ATP degradation pathway, such as hypoxanthine, could be of greater pathogenetic importance [5]. Unfortunately, these substances can not be measured by  $^{31}\text{P}$  MRS because they do not contain phosphorus. Hypoxanthine levels could be measured in pre-implantation kidney graft biopsies by techniques such as high performance liquid chromatography. Results of such measurements, however, would not be available rapidly enough to guide clinical decisions in renal transplantation.

At this point, it should also be noted that the occurrence of ATN in transplanted kidneys is determined by a multitude of factors of which several take place at the time of or even after implantation [12]. These include the volume status of the receiver, the use of scavengers like mannitol, the administration of calcium entry blockers and the skill of the surgeon [13]. Moreover, the diagnosis of ATN after transplantation is generally based on clinical findings, and often not proven by histology. Early rejection and technical problems may imitate ATN. Although we did our best to exclude these patients from our study, these factors will limit the predictive value of any test which is performed before implantation.

Our observation of a graded decay of the PME/Pi ratio during cold storage of kidneys (Figs. 3 and 4) disagrees with a study of Bretan et al [7], who failed to find a relation between cold ischemia time and PME/Pi ratio in human kidneys. The discrepancy between the two studies may be related to the difference in preservation fluid. We used a phosphate free solution, whereas Bretan et al studied kidney grafts perfused with a phosphate containing solution (Collins-2). This would agree with the observation that these authors did find a relation between cold ischemia and PME/Pi ratio in a study in dogs, in which they used a phosphate free preservation fluid as in the present study [7, 14].

Preliminary data published by Pomer, Hull and Mohring agree with the notion of a gradual decay of high-energy phosphates in human kidney grafts [15].

A further difference between the two studies in humans is that the mean PME/Pi ratio in HBD-derived grafts reported by Bretan et al was lower ( $0.62 \pm 0.45$ ) than in our study ( $1.65 \pm 0.41$ ). This confirms observations of Lietzenmayer et al [9] and Ciancabilla et al [10], who found an inverse relation between the PME/Pi ratio and the phosphate content of various preservation fluids. As it has been shown that high phosphate signals originating from the preservation solution may interfere with a correct determination of the concentration of renal high-energy phosphate metabolites [14], it is conceivable that the use of a phosphate free preservation fluid could improve the performance of  $^{31}\text{P}$  MRS in predicting ATN. However, we could not confirm this notion: the sensitivity (0.67) and specificity (0.91) of the PME/Pi ratio in predicting ATN were similar as those reported by Bretan et al [7] in kidneys preserved in a phosphate containing solution (0.73 and 0.84, respectively).

In view of the general relation between the PME/Pi ratio and the occurrence of ATN, one might consider to avoid implanting kidneys with a low PME/Pi ratio into patients with other risk factors, like a poor HLA match, a high level of lymphocytotoxic antibodies or preexisting cardiovascular disease. More importantly, in view of the possible harmful effect of cyclosporin A in grafts suffering from ATN [16], this drug should perhaps be avoided lower dosed in recipients of kidneys with a low pre-transplant PME/Pi ratio. Whether such an approach will improve the clinical outcome of kidney transplantations remains, however, to be established.

In conclusion, we found a general relation between the level of the pre-transplant PME/Pi ratio measured by  $^{31}\text{P}$  MRS and the development of ATN in kidney grafts preserved in a phosphate free solution. At present, the predictive value of this method (36%) is too small to predict development of ATN reliably in individual cases. However, extrapolation of the PME/Pi ratio to the time of nephrectomy may improve the usefulness of the method.

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